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(54) Title: COMBINATION OF A MACROLIDE AND A LOCAL ANESTHETIC FOR THE TREATMENT OF DERMATOLOGICAL DISEASES

(57) Abstract: Synergistic combinations of a macrolide T-cell immunomodulator or immunosuppressant such as 33-epichloro-33-desoxyascomycin and a local anaesthetic such as lidocaine, polidocanol or prilocaine are provided, which are useful in particular in the treatment of dermatological diseases such as atopic, contact or seborrhoeic dermatitis, psoriasis, acne, rosacea, post-peel, pruritus, skin burning, or itching; and associated pain.

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COMBINATION OF A MACROLIDE AND A LOCAL ANESTHETIC FOR THE TREATMENT OF DERMATOLOGICAL DISEASES

The invention relates to pharmaceutical compositions, for use in particular in the treatment of skin diseases. It concerns a pharmaceutical composition comprising a macrolide T-cell immunomodulator or immunosuppressant and a local anaesthetic.

It has now been found that, surprisingly, macrolide T-cell immunomodulators and immunosuppressants, when used in combination with local anaesthetics, act synergistically, resulting in a potentiation of pharmacological activity, such that effective beneficial, especially anti-dermatitis activity and pain relief is seen upon co-administration at dosages which would be well below the effective dosages administered individually.

The invention thus concerns novel pharmaceutical compositions comprising a **macrolide T-cell immunomodulator or immunosuppressant** in association or combination with a **local anaesthetic**, hereinafter briefly named "the compositions of the invention".

A macrolide T-cell immunomodulator or immunosuppressant is to be understood herein as being a T-cell immunomodulator or T-cell immunosuppressant which has a macrocyclic compound structure including a lactone or lactam moiety. While it preferably has at least some T-cell immunomodulating or immunosuppressant activity, it may also exhibit concomitantly or predominantly further pharmaceutical properties, such as anti-inflammatory activity.

A local anaesthetic is to be understood herein as being a compound other than benzyl alcohol which induces a locally limited, reversible condition of peripheral, pain-transmitting nerves or nerve endings which is associated with partial or complete lack of excitability or conducibility.

The compositions of the invention may be adapted for systemic use as regards the immunomodulator or immunosuppressant component, e.g. oral or intravenous, or for topical use for both components; however, they are preferably both adapted for topical use. They are useful for the known indications of the particular active agents incorporated therein. They are particularly indicated for use in dermatological diseases, e.g. dermatological diseases which have an inflammatory component or involve inflammatory complications, such as atopic,

contact or seborrhoeic dermatitis, psoriasis, acne, rosacea, post-peel, pruritus, skin burning, or itching; and associated pain.

A suitable **macrolide T-cell immunomodulator or immunosuppressant** is for example an FKBP12-binding calcineurin inhibitor or mitogen-activated kinase modulator or inhibitor, in particular an **asco-** or **rapamycin**. It preferably is an ascomycin. While the macrolide preferably has at least some calcineurin- or mitogen-activated kinase modulating or inhibiting activity, it may also exhibit concomitantly or predominantly further pharmaceutical properties, such as antiinflammatory activity. It preferably is a compound, e.g. an ascomycin, having rather long-acting activity relatively to other members of the same structural class, e.g. it is metabolically degraded slowly to inactive products.

An asco- or rapamycin is to be understood as asco- or rapamycin as such, or a derivative thereof. An asco- or rapamycin derivative is to be understood as being an antagonist, agonist or analogue of the parent compound which retains the basic structure and modulates at least one of the biological, for example immunological properties of the parent compound.

An "anti-inflammatory ascomycin derivative" is defined herein as an ascomycin derivative that exhibits pronounced anti-inflammatory activity in e.g. animal models of allergic contact dermatitis but has only low potency in suppressing systemic immune response, namely, which has a minimum effective dose (MED) of up to a concentration of about 0.04 % w/v in the murine model of allergic contact dermatitis upon topical administration, while its potency is at least 10 times lower than for tacrolimus (MED 14 mg/kg) in the rat model of allogeneic kidney transplantation upon oral administration (Meingassner, J.G. et al., Br. J. Dermatol. 137 [1997] 568-579; Stuetz, A. Seminars in Cutaneous Medicine and Surgery 20 [2001] 233-241). Such compounds are preferably lipophilic.

Suitable **ascomycins** are e.g. as described in EP 184162, EP 315978, EP 323042, EP 423714, EP 427680, EP 465426, EP 474126, WO 91/13889, WO 91/19495, EP 484936, EP 523088, EP 532089, EP 569337, EP 626385, WO 93/5059 and WO 97/8182;
in particular:

- **ascomycin**;
- **tacrolimus** (FK506; Prograf^{R});

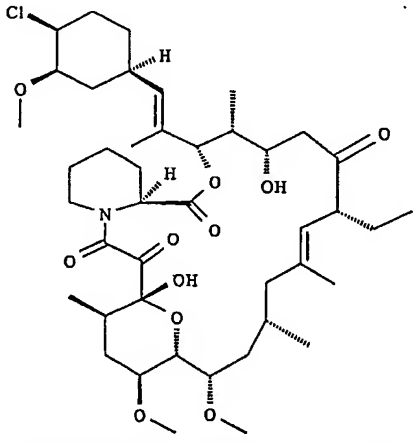
- **imidazolylmethoxyascomycin** (WO 97/8182 in Example 1 and as compound of formula I);
- **32-O-(1-hydroxyethylindol-5-yl)ascomycin** (L-732531) (Transplantation 65 [1998] 10-18, 18-26, on page 11, Figure 1; and
- **(32-desoxy-32-epi-N1-tetrazolyl)ascomycin** (ABT-281) (J.Invest.Dermatol. 12 [1999] 729-738, on page 730, Figure 1);

preferably:

- {1R,5Z,9S,12S-[1E-(1R,3R,4R)],13R,14S,17R,18E,21S,23S,24R,25S,27R}-17-ethyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0(4,9)]octacos-5,18-diene-2,3,10,16-tetraone (Example 8 in EP 626385),
  hereinafter referred to as "**5,6-dehydroascomycin**";
- {1E-(1R,3R,4R)]1R,4S,5R,6S,9R,10E,13S,15S,16R,17S,19S,20S}-9-ethyl-6,16,20-trihydroxy-4-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-15,17-dimethoxy-5,11,13,19-tetramethyl-3-oxa-22-azatricyclo[18.6.1.0(1,22)]heptacos-10-ene-2,8,21,27-tetraone (Examples 6d and 71 in EP 569337), hereinafter referred to as "**ASD 732**";

and especially

- **pimecrolimus** (INN recommended) (ASM981; Elidel™), i.e. {[1E-(1R,3R,4S)]1R,9S,12S, 13R,14S,17R,18E, 21S,23S,24R,25S,27R}-12-[2-(4-chloro-3-methoxycyclohexyl)-1-methylvinyl]-17-ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28,dioxa-4-azatricyclo [22.3.1.0(4,9)]octacos-18-ene-2,3,10,16-tetraone,
  of formula I



(Example 66a in EP 427680), hereinafter also referred to as "**33-epichloro-33-desoxyascomycin**".

Suitable anti-inflammatory ascomycin derivatives are e.g.: (32-desoxy-32-epi-N1-tetrazolyl)ascomycin (ABT-281); 5,6-dehydroascomycin; ASD 732; and pimecrolimus.

Suitable **rapamycins** are e.g. as described in USP 3'929'992, WO 94/9010 and USP 5'258'389, preferably **sirolimus** (rapamycin; Rapamune^R) and **everolimus** (RAD001; Certican^R).

A suitable **local anaesthetic** is for example an aminoester or aminoamide; it is e.g.:

- benzocaine (4-aminobenzoic acid ethyl ester);
- bufexamac;
- bupivacaine (1-n-butyl-2',6'-dimethyl-2-piperidinecarboxanilide);
- dibucaine hydrochloride (cinchocaine; 2-butoxy-N-[2-(diethylamino)ethyl]-4-quinolinecarboxamide monohydrochloride);
- dimethisoquin (quinisocaine; 3-butyl-1-[2-(dimethylamino)ethoxy]isoquinoline);
- dyclonine [Dyclone^R; 4-n-butoxy-β-(1-piperidyl)propiophenone];
- etidocaine [2-(ethylpropylamine)-2',6'-butyroxylidide];
- lidocaine (lignocaine; Xylocaine^R; ω-diethylamino-2,6-dimethylacetanilide);
- mepivacaine (dl-N-methylpipecolic acid 2,6-dimethylanilide);
- myrtecaine (Nopoxamine^R; 2-[2-(6,6-dimethyl-2-morpinen-2-yl)ethoxy]triethylamine);
- polidocanol (Thesit^R; hydroxypolyethoxydodecane);
- pramoxine (pramocaine; p-butoxyphenyl γ-morpholinopropyl ether);
- prilocaine (propitocaine; α-propylamino-2-methylpropionanilide);
- procaine (p-aminobenzoyldiethylaminoethanol);
- tetracaine (p-butylaminobenzoyl-2-dimethylaminoethanol hydrochloride);

preferably polidocanol and prilocaine, especially lidocaine.

Subgroups of compositions of the invention comprise a macrolide T-cell immunomodulator or immunosuppressant, preferably an anti-inflammatory ascomycin derivative as defined above, especially pimecrolimus, in combination or association with a local anaesthetic other than prilocaine and/or lidocaine.

In a further subgroup of compositions of the invention the macrolide T-cell immunomodulator or immunosuppressant is other than tacrolimus. In a further subgroup it is other than tacrolimus and sirolimus. In a further subgroup it is other than tacrolimus, sirolimus and ascomycin.

A particularly preferred composition of the invention is pimecrolimus in association or combination with lidocaine.

The local anaesthetic may be e.g. an injectable or, preferably, a compound indicated for topical use.

Preferred for use in the treatment of conditions where inflammation is involved are compositions of the invention wherein one or both components possess some degree of inherent anti-inflammatory activity. Particularly preferred are compositions comprising an ascomycin in combination with a local anaesthetic, especially 33-epichloro-33-desoxy-ascomycin in combination with polidocanol, lidocaine or prilocaine. The inflammatory condition is e.g. atopic, contact or seborrhoeic dermatitis, psoriasis, acne, rosacea, post-peel, pruritus, skin burning, or itching; and associated pain.

"Treatment" as used herein includes prevention, namely prophylactic as well as curative treatment.

The local anaesthetic component is administered normally topically; the macrolide T-cell immunomodulator or immunosuppressant may be administered together with the local anaesthetic, normally topically, or separately, either topically or systemically. Preferred is topical administration of both components.

Synergy is e.g. calculated as in Berenbaum, Clin. Exp. Immunol. 28 (1977) 1, using an interaction term to correct for differences in mechanism between the two drugs, as described in Chou et al., Transpl. Proc. 26 (1994) 3043. The index of synergy is calculated as:

$$\frac{\text{dose of A}}{A_E} + \frac{\text{dose of B}}{B_E} + \frac{(\text{dose of A}) \times (\text{dose of B})}{A_E \times B_E}$$

in which the doses of the compounds A and B represent those used in a particular combination, and A_E and B_E are the individual doses of A and B respectively giving the same effect. If the result is less than 1, there is synergy; if the result is 1, the effect is additive; if the result is greater than 1, A and B are antagonistic. By plotting an isobologram of dose of A / A_E

vs. dose of B / B_E the combination of maximum synergy can be determined. The synergistic ratio expressed in terms of the ratio by weight of the two compositions at synergistic amounts along the isobologram, especially at or near the point of maximum synergy, can then be used to determine formulations containing an optimally synergistic ratio of the two compounds.

Activity may e.g. be determined in known assay models for testing the pharmacological activity of the individual components of the compositions.

The invention also provides products and methods for co-administration of a macrolide T-cell immunomodulator or immunosuppressant, e.g. 33-epichloro-33-desoxy-ascomycin or 5,6-dehydroascomycin, and a local anaesthetic, e.g. polidocanol, lidocaine or prilocaine, at synergistically effective dosages, e.g.:

- a method of treatment or prevention of a dermatological disease such as atopic, contact or seborrhoeic dermatitis, psoriasis, acne, rosacea, post-peel, pruritus, skin burning, or itching, and associated pain, in a subject suffering from or at risk for such condition, comprising co-administering synergistically effective amounts of a composition of the invention;
- the use of a macrolide T-cell immunomodulator or immunosuppressant in the manufacture of a medicament for co-administration in synergistically effective amounts with a local anaesthetic;
- the use of a local anaesthetic in the manufacture of a medicament for co-administration in synergistically effective amounts with a macrolide T-cell immunomodulator or immunosuppressant;
- a kit of parts comprising a macrolide T-cell immunomodulator or immunosuppressant and a local anaesthetic in separate unit dosage forms, preferably wherein the unit dosage forms are suitable for administration of the component compounds in synergistically effective amounts, together with instruction for use, optionally with further means for facilitating compliance with the administration of the component compounds, e.g. a label or drawings;
- the use of a macrolide T-cell immunomodulator or immunosuppressant in the manufacture of a pharmaceutical kit which is to be used for facilitating co-administration with a local anaesthetic;
- the use of a local anaesthetic in the manufacture of a pharmaceutical kit which is to be used for facilitating co-administration with a macrolide T-cell immunomodulator or immunosuppressant;

- a macrolide T-cell immunomodulator or immunosuppressant and a local anaesthetic as a combined pharmaceutical preparation for simultaneous, separate or sequential use, preferably in synergistically effective amounts, e.g. for the treatment or prevention of a dermatological disease such as atopic, contact or seborrhoeic dermatitis, psoriasis, acne, rosacea, post-peel, pruritus, skin burning, or itching; and associated pain;
- a pharmaceutical composition comprising a macrolide T-cell immunomodulator or immunosuppressant in combination or association with a local anaesthetic, e.g. in synergistically effective amounts, together with at least one pharmaceutically acceptable diluent or carrier, e.g. for use in treatment or prevention of a dermatological disease such as atopic, contact or seborrhoeic dermatitis, psoriasis, acne, rosacea, post-peel, pruritus, skin burning, or itching; and associated pain; and
- a process for the preparation of a composition of the invention comprising mixing a macrolide T-cell immunomodulator or immunosuppressant and a local anaesthetic, in combination or association with at least one pharmaceutically acceptable diluent or carrier.

By "synergistically effective amounts" is meant an amount of macrolide T-cell immunomodulator or immunosuppressant and an amount of local anaesthetic which are individually below their respective effective dosages for a relevant indication, but which are pharmaceutically active on co-administration, e.g. in a synergistic ratio, for example as calculated above. Furthermore, "synergistically effective amounts" may mean an amount of macrolide T-cell immunomodulator or immunosuppressant and an amount of local anaesthetic which are individually equal to their respective effective dosages for a relevant indication, and which result in a more than additive effect.

The molar amount of macrolide T-cell immunomodulator or immunosuppressant present is from roughly similar to, to significantly less than the amount of local anaesthetic, preferably half as much or less. Synergistic ratios of macrolide T-cell immunomodulator or immunosuppressant to local anaesthetic by weight are thus suitably from about 10:1 to about 1:50, preferably from about 5:1 to about 1:20, most preferably from about 1:1 to about 1:15, e.g. about 1:12.

The compositions of the invention can be administered as a free combination, e.g. for separate systemic and topical administration of the two components, or can be formulated into a fixed combination, preferably for topical administration of both components, which greatly enhances the convenience for the patient.

Absolute dosages of the compounds will vary depending on a number of factors, e.g. the individual, the route of administration, the desired duration, the rate of release of the active agent and the nature and severity of the condition to be treated. For example, the amount of active agents required and the release rate thereof may be determined on the basis of known in vitro and in vivo techniques, determining how long a particular active agent concentration in the blood plasma remains at an acceptable level for a therapeutic effect.

For example, in prevention and treatment of a dermatological disease such as atopic or contact dermatitis, itching, or pruritus, an initial dosage of about 2-3 times the maintenance dosage is suitably administered, followed by a daily dosage of about 2-3 times the maintenance dosage for a period of from one to two weeks, and subsequently the dose is gradually tapered down at a rate of about 5 % per week to reach the maintenance dosage. In general, synergistically effective amounts of 33-epichloro-33-desoxyascomycin on oral administration for use in prevention and treatment of atopic, contact or seborrhoeic dermatitis, psoriasis, acne, rosacea, post-peel, pruritus, skin burning, or itching, and associated pain, in larger animals, e.g. man, are amounts of 33-epichloro-33-desoxyascomycin of up to about 2 mg/kg/day, e.g. from about 0.01 mg/kg/day to about 2 mg/kg/day, preferably about 0.5 mg/kg/day, in combination or co-administration with topically effective amounts of polidocanol, lidocaine or prilocaine, in a synergistic ratio as described.

By "co-administration" is meant administration of the components of the compositions of the invention together or at substantially the same time, e.g. within fifteen minutes or less, either in the same vehicle or in separate vehicles.

The compositions of the invention include compositions suitable for administration by any conventional route, in particular compositions suitable for administration either enterally, for example, orally, e.g. in the form of solutions for drinking, tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions; or topically, e.g. for the

treatment of inflammatory conditions of the skin or mucosae, e.g. in the form of a dermal cream, ointment, ear drops, mousse, shampoo, solution, lotion, gel, emulgel or like preparation, e.g. in a concentration of from about 0.1 % to about 5 % by weight of each component, especially in combination or association with penetration enhancing agents, as well as for application to the eye, e.g. in the form of an ocular cream, gel or eye-drop preparation, for treatment of inflammatory conditions of the lungs and airways, e.g. in the form of inhalable compositions, and for mucosal application, e.g. in the form of vaginal tablets.

The compositions of the invention are suitably emulsions, microemulsions, emulsion preconcentrates or microemulsion preconcentrates, or solid dispersions, especially water-in-oil microemulsion preconcentrates or oil-in-water microemulsions, comprising the macrolide T-cell immunomodulator or immunosuppressant and the local anaesthetic in a synergistic ratio.

The compositions of the invention can be prepared in conventional manner, e.g. by mixing a macrolide T-cell immunomodulator or immunosuppressant and a local anaesthetic, in combination or association with at least one pharmaceutically acceptable diluent or carrier.

The active agent components may be in free form or pharmaceutically acceptable salt form as appropriate.

While the present invention primarily contemplates combination or association of just two pharmaceutically active components, it does not exclude the presence of further active agents, e.g. one further active agent, as far as they do not contradict the purpose of the invention.

The following Examples illustrate the invention. The compounds are in free, i.e. neutral or base form unless specified otherwise.

Example 1: Cream

Component	Amount (g)
33-Epichloro-33-desoxyascomycin	1.00
lidocaine hydrochloride	2.00
triglycerides, medium chain	15.00
oleyl alcohol	10.00
sodium cetylstearyl sulfate	1.00
cetyl alcohol	4.00
stearyl alcohol	4.00
glyceryl monostearate	2.00
Methylparaben**	0.20
Propylparaben***	0.10
propylene glycol	5.00
citric acid	0.05
sodium hydroxide	*
water	ad 100.0

* amount required to adjust pH to 5.5
** p-hydroxybenzoic acid methylester
*** p-hydroxybenzoic acid propylester

The preparation follows the conventional manufacturing procedures for an emulsion. 33-Epichloro-33-desoxyascomycin is added to the heated homogeneous oily phase which contains triglycerides medium chain, oleyl alcohol, sodium cetylstearyl sulfate, cetyl alcohol , stearyl alcohol and glyceryl monostearate. In parallel, the water phase containing lidocaine hydrochloride, the Parabens, propylene glycol, citric acid and sodium hydroxide is heated at the same temperature as the oily phase. The oily phase is added to the water phase and homogeneisation is performed. The resultant cream is cooled to room temperature.

Example 2: Cream

The composition and its preparation are as for Example 1, except that benzyl alcohol 1.00 g is used in place of the Parabens.

Claims:

1. A pharmaceutical composition comprising a macrolide T-cell immunomodulator or immunosuppressant in combination or association with a local anaesthetic, together with at least one pharmaceutically acceptable diluent or carrier.

2. A composition according to claim 1 comprising 33-epichloro-33-desoxyascomycin in combination or association with lidocaine, polidocanol or prilocaine.

3. A method of treatment of a dermatological disease such as atopic, contact or seborrhoeic dermatitis, psoriasis, acne, rosacea, post-peel, pruritus, skin burning, or itching, and associated pain, in a subject suffering from or at risk for such condition, comprising co-administering a synergistically effective amount of a composition according to claim 1.

4. A process for the preparation of a composition according to claim 1 comprising mixing a macrolide T-cell immunomodulator or immunosuppressant and a local anaesthetic, in combination or association with at least one pharmaceutically acceptable diluent or carrier.

5. A kit of parts comprising a macrolide T-cell immunomodulator or immunosuppressant and a local anaesthetic in separate unit dosage forms, together with instructions for use.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/436 A61K31/167 A61K31/08 A61P17/00
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE WPI Section Ch, Week 200436 Derwent Publications Ltd., London, GB; Class B03, AN 2004-377036 XP002286183 & CN 1 478 476 A (SUN W) 3 March 2004 (2004-03-03) abstract -----	1,4
X	DATABASE WPI Section Ch, Week 200240 Derwent Publications Ltd., London, GB; Class B05, AN 2002-363575 XP002286184 & CN 1 338 290 A (HUANG J) 6 March 2002 (2002-03-06) abstract ----- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EPODOC EUROPEAN PATENT OFFICE, THE HAGUE, NL; 3 September 1997 (1997-09-03), XP002286182 abstract & CN 1 158 258 A (LI ZHIHUI) 3 September 1997 (1997-09-03)	1-5
X	VIKTORINOVA M: "New antibiotic primycin in the treatment of pyodermas and acne" CESKO-SLOVENSKA DERMATOLOGIE 1998 CZECH REPUBLIC, vol. 73, no. 5, 1998, pages 153-157, XP009032474 ISSN: 0009-0514 abstract	1-5
X	WO 02/062353 A (WHARTON MARIE MADELINE) 15 August 2002 (2002-08-15) claims 1,2,5	1,3,4
X	US 5 064 815 A (SCHREINER NEE KOVATS ENIKOE ET AL) 12 November 1991 (1991-11-12) example 21	1,4
X	GB 766 245 A (LILLY CO ELI) 16 January 1957 (1957-01-16) page 2, lines 52-83	1,4
X	DATABASE WPI Section Ch, Week 200318 Derwent Publications Ltd., London, GB; Class B05, AN 2003-181627 XP002286185 & RU 2 195 279 C1 (UNIV TULA) 27 December 2002 (2002-12-27) abstract	1,4
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A	US 6 120 792 A (JUNI JACK E) 19 September 2000 (2000-09-19) column 1, lines 10-35 column 3, lines 21-43; claims 1,4,5	1-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/003515

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 3 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/003515

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